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Commentary

Trends in Quantitative Cancer Risk Assessment

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Quantitative cancer risk assessment is a dynamic field, more closely coupled to rapidly advancing biomedical research than ever before. Six areas of change and growth are identified: expansion from models of cancer initiation to a more complete picture of the total carcinogenic process; trend from curve-fitting to biologically based models; movement from upper-bound estimates to best estimates, with a more complete treatment of uncertainty; increased consideration of the role of susceptibility; growing development of expert systems and decision support systems; and emerging importance of risk communication.

Because quantitative cancer risk assessment has been woven into the fabric of government regulatory processes, one might expect to find its methods carved into bureaucratic stone. The papers on cancer risk modeling at this symposium attest that this is not the case; indeed, quantitative cancer risk assessment remains a dynamic area of research. Risk analysts with varied academic backgrounds continue to improve or replace models that sometimes stem back to the 1950s. Risk assessment is probably more closely coupled now to rapidly advancing biomedical research than it has ever been before.

First, early cancer risk assessment models focused almost entirely on models of cancer initiation, e.g., the one-hit model. There is a growing trend to expand assessment models to a more complete picture of the total process, including exposure, metabolic activation, pharmacokinetics, biologically effective dose, initiation, cellular proliferation, promotion, immunocontrol, suppression, and progression. In some cases, models of individual processes are linked together for assessment, while in others several processes are incorporated in a single model. This largely reflects better understanding of carcinogenic processes and the ability to better measure some of the intermediate steps. Progress in model development must be made in step with increasing availability of data. This progress was illustrated in the papers presented by Chen (*1*), Hattis (*2*), and Wilson (*3*) at this symposium.

Second, closely related to the trend toward including a more complete biological picture is a trend from empirical models that basically involve curve fitting to more biologically based models. The expanding interest in physiologically based pharmacokinetic models (*4*) and in more biologically descriptive cancer models developed by Moolgavkar and colleagues that explicitly incorporate the kinetics of tissue growth and development (*5–7*) illustrate this trend. Hattis' presentation showed applications of the former, while Wilson's paper (*3*) has provided a detailed history of the changes in high-dose to low-dose extrapolation modeling from the multistage models of the 1950s (*8*) to the more general Moolgavkar model.

Chen's presentation (*1*) illustrated the increasing ability to model the biology of carcinogenic processes in a case that shows the dependency of modeling on new biomedical research measurements. This case may also indicate the reverse flow, that understanding derived from models can lead to revision of experimental designs. Models of this kind may eventually allow risk assessment and regulatory standards to treat carcinogens that have different mechanisms of action more appropriately, thus leading to more realistic risk assessments.

Although it may not seem so at first, a trend toward more detailed biologically based models is not inconsistent with the simpler "model free" approach proposed by Krewski's paper (*9*) at this symposium. If sufficient data are not available to model adequately the full process, it may be better to use an extremely simple approach to make preliminary estimates, rather than to apply a sophisticated model to a rudimentary data set.

Third, there is a movement from reliance on upper-bound estimates to best estimates, with a more complete treatment of uncertainty and appropriate propagation of uncertainty through the different stages of analysis. Reliance on upper-bound estimates alone can distort perceptions of risk, leading unknowingly to excessively conservative actions. Aspects of uncertainty were discussed in several papers at this symposium. Mazumdar (*10*), in particular, presented investigations of joint confidence region calculations and of robustness in the multistage model that illustrate this increasing focus on understanding uncertainty in the estimates.

Fourth, there is increasing consideration of variation in cancer susceptibility within the exposed population. Louis (*11*), Perera (*12*), and Rockette (*13*) discussed this topic. Krewski (*9*) examined the often raised concept that heterogeneity in the population leads to a superlinear dose-response curve for the

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combined population. He concluded that this result was possible only under highly improbable mixes of subgroup susceptibility.

Fifth, one emerging area was not covered by any of the speakers. That is the growing development of expert systems and decision support systems for use in risk assessment. Some applications in this area have recently been described (*14*). The topic was the subject of several papers at the 1988 annual meeting of the Society for Risk Analysis and has received considerable attention from the Environmental Protection Agency's Office of Solid Waste and Emergency Response (*15*).

Sixth, the emerging field of risk communication was mentioned briefly in the session on Applications to Hazardous Waste Sites. After over two decades of quantitative risk assessment for radiation and chemical carcinogens, we have discovered that the public does not care if the risk is 10^{-3} or 10^{-23}. These numbers do not have any meaning for them, and I sometimes wonder how much real meaning they have for even the professionals in the field. Despite a lack of concern with the specifics of quantification, however, people are concerned about health risks more than ever. I am convinced that feedback from risk communication will change what we address in risk analysis, how the analysis is done, and how the results are presented.

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